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Applicants:

Randy S. Bethiel et al.

Application No.:

10/700,936

## AMENDMENTS TO THE CLAIMS

Please replace all prior versions and listings of claims with the amended claims as follows:

1. (Previously presented) A compound of formula I:

or a pharmaceutically acceptable salt thereof, wherein:

 $W^1$  is nitrogen or CH,  $W^2$  is nitrogen or C-(U)<sub>p</sub>R<sup>U</sup>, and  $W^3$  is nitrogen or C-(V)<sub>q</sub>R<sup>V</sup>; p and q are each independently 0 or 1;

R<sup>U</sup> and R<sup>V</sup> are each independently R or Ar<sup>1</sup>;

U and V are each independently a bond or a C<sub>1-6</sub> alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by CO, CO<sub>2</sub>, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO<sub>2</sub>, NRCONR, SO, SO<sub>2</sub>, NRSO<sub>2</sub>, SO<sub>2</sub>NR, NRSO<sub>2</sub>NR, O, S, or NR;

each occurrence of R is independently hydrogen or an optionally substituted C<sub>1</sub>-C<sub>4</sub> aliphatic, or two R bound to the same nitrogen atom are optionally taken together with the nitrogen atom to form a 3-7 membered saturated, partially unsaturated, or fully unsaturated ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ar<sup>1</sup> is a 5-7 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or

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sulfur; wherein Ar<sup>1</sup> is optionally substituted with m independent occurrences of Z-R<sup>5</sup>; wherein m is 0-5, Z is a bond or is a C<sub>1</sub>-C<sub>6</sub> alkylidene chain wherein up to two methylene units of Z are optionally replaced by CO, CO<sub>2</sub>, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO<sub>2</sub>, NRCONR, SO, SO<sub>2</sub>, NRSO<sub>2</sub>, SO<sub>2</sub>NR, NRSO<sub>2</sub>NR, O, S, or NR; and each occurrence of R<sup>5</sup> is independently hydrogen, an optionally substituted aliphatic, heteroaliphatic, aryl or heteroaryl group, halogen, NO<sub>2</sub>, CN, OR, SR, N(R)<sub>2</sub>, NRCOR, NRCON(R)<sub>2</sub>, NRCO<sub>2</sub>R, COR, CO<sub>2</sub>R, OCOR, CON(R)<sub>2</sub>, OCON(R)<sub>2</sub>, SOR, SO<sub>2</sub>R, SO<sub>2</sub>N(R)<sub>2</sub>, NRSO<sub>2</sub>R, NRSO<sub>2</sub>N(R)<sub>2</sub>, COCOR, or COCH<sub>2</sub>COR;

R<sup>1</sup> and R<sup>2</sup> are taken together and fused to ring B to form a heterocyclic moiety selected from one of formulae (a) through (f):

wherein each occurrence of R<sup>X</sup> is independently hydrogen, QR, or Q<sub>n</sub>Ar<sup>1</sup>; n is zero or one; and Q is an optionally substituted C<sub>1-4</sub> alkylidene chain wherein one methylene unit of Q is optionally replaced by CO, CO<sub>2</sub>, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO<sub>2</sub>, NRCO<sub>2</sub>, NRCO<sub>2</sub>, NRCO<sub>2</sub>, SO<sub>2</sub>NR, NRSO<sub>2</sub>NR, O, S, or NR;

R<sup>3</sup> is hydrogen, halogen, QR, Q<sub>n</sub>CN, Q<sub>n</sub>NO<sub>2</sub>, or Q<sub>n</sub>Ar<sup>1</sup>; and R<sup>4</sup> is Ar<sup>1</sup>, or T-Ar<sup>1</sup>;

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wherein T is a C<sub>1-2</sub> alkylidene chain wherein one methylene unit of T is optionally replaced by CO, CO<sub>2</sub>, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO<sub>2</sub>, NRCONR, SO, SO<sub>2</sub>, NRSO<sub>2</sub>, SO<sub>2</sub>NR, NRSO<sub>2</sub>NR, O, S, or NR.

- 2. (Previously presented) The compound of claim 1, wherein  $R^1$  and  $R^2$  taken together form the heterocyclic moiety of formula (a) and  $R^X$  is hydrogen or optionally substituted  $C_{1-6}$  aliphatic.
- 3. (Original) The compound of claim 1, wherein  $R^X$  is hydrogen, methyl, ethyl, propyl, n-butyl, tert-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl,  $C_{1\text{-}6}$ alkyl substituted with  $N(R)_2$ , or  $C_{1\text{-}6}$ alkyl substituted with  $Ar^1$ .
- 4. (Original) The compound of claim 1, wherein  $R^X$  is hydrogen, methyl, or  $C_{1-2}$ alkyl substituted with a group selected from optionally substituted phenyl, pyridyl, morpholino, piperidinyl, or piperazinyl.
- 5. (Original) The compound of claim 1, wherein R<sup>3</sup> is hydrogen, halogen, QR or QAr<sup>1</sup>, wherein Q is a C<sub>1-3</sub> alkylidene chain wherein one methylene unit of Q is optionally replaced by -O-, -S-, -NHCO-, or -NR-, and Ar<sup>1</sup> is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
- 6. (Original) The compound of claim 1, wherein R<sup>3</sup> is hydrogen, OH, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, NHCOMe, NH<sub>2</sub>, NH(C<sub>1-4</sub> aliphatic), N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, O(CH<sub>2</sub>)<sub>2</sub>morpholin-4-yl, O(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, O(CH<sub>2</sub>)<sub>2</sub>NH(C<sub>1-4</sub> aliphatic), O(CH<sub>2</sub>)<sub>2</sub>N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, Br, Cl, or F.
- 7. (Original) The compound of claim 1, wherein R<sup>3</sup> is hydrogen.

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- 8. (Original) The compound of claim 1, wherein R<sup>4</sup> is a 6-membered saturated, partially unsaturated, or aryl ring having 0-3 nitrogens, a 9-10 membered bicyclic aryl ring having 0-2 nitrogen atoms, or a 5 membered heteroaryl ring having 2-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each ring is optionally substituted.
- 9. (Original) The compound of claim 1. wherein R<sup>4</sup> is optionally substituted phenyl, cyclohexyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, indazolyl, or benzimidazolyl.
- 10. (Original) The compound of claim 1, wherein R<sup>4</sup> is an optionally substituted phenyl group.
- 11. (Original) The compound of claim &, wherein each occurrence of Z is independently a bond or a  $C_{1-4}$  alkylidene chain wherein one methylene unit of Z is optionally replaced by O-, -S-, -SO<sub>2</sub>-, or -NH-; and each occurrence of  $R^5$  is independently hydrogen,  $C_{1-6}$  aliphatic, halogen, NO<sub>2</sub>, OR, N(R)<sub>2</sub>, or optionally substituted phenyl, pyridyl, or pyrimidinyl.
- 12. (Previously presented) The compound of claim 8, wherein each occurrence of ZR<sup>5</sup> is independently Cl, F, Br, methyl, ethyl, t-butyl, isopropyl, cyclopropyl, nitro, CN, OMe, OEt, CF<sub>3</sub>, NH<sub>2</sub>, phenyl, benzyl, benzyloxy, OH, methylenedioxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, CO<sub>2</sub>Me, phenoxy, O-pyridinyl, SO<sub>2</sub>phenyl, nitrophenoxy, aminophenoxy, S-dimethylpyrimidine, NHphenyl, NH-methoxyphenyl, pyridinyl, phenol, chloro-fluoro-phenyl, dimethylaminophenyl, CF<sub>3</sub>-phenyl, dimethylphenyl, chlorophenyl, fluorophenyl, methoxyphenoxy, chlorophenoxy, ethoxyphenoxy, and fluorophenoxy.
- 13. (Original) The compound of claim 1, wherein  $(U)_p R^U$  and  $(V)_q R^V$  are each independently hydrogen, halogen, NO<sub>2</sub>, CN, OR, SR or N(R)<sub>2</sub>, or C<sub>1-4</sub>aliphatic optionally substituted with oxo, OR, SR, N(R)<sub>2</sub>, halogen, NO<sub>2</sub> or CN.

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- 14. (Original) The compound of claim 1, wherein  $(U)_p R^U$  and  $(V)_q R^V$  are each independently hydrogen, Me, OH, or OMe.
- 15. (Original) The compound of claim 1, wherein W<sup>1</sup> is N or CH and compounds have the structure of Formula Ia or Ib:

or a pharmaceutically acceptable salt thereof.

16. (Previously presented) The compound of claim 15, wherein R<sup>4</sup> is an optionally substituted phenyl group and compounds have the structure of Formula IIa or IIb:

HN 
$$(\mathbb{Z}\mathbb{R}^5)_{m}$$

HN  $\mathbb{R}^1$ 
 $\mathbb{R}^3$ 

HN  $\mathbb{R}^1$ 
 $\mathbb{R}^3$ 

HN  $\mathbb{R}^1$ 
 $\mathbb{R}^3$ 

HN  $\mathbb{R}^1$ 
 $\mathbb{R}^1$ 
 $\mathbb{R}^3$ 

Hb

or a pharmaceutically acceptable salt thereof.

17. (Previously presented) The compound of claim 16, wherein R<sup>3</sup> is hydrogen, and compounds have the structure of Formula IIIa or IIIb:

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HN 
$$(ZR^5)_m$$

HN  $(ZR^5)_m$ 
 $R^1$ 
 $R^2$ 

IIIa

or a pharmaceutically acceptable salt thereof.

18. (Previously presented) The compound of claim 16, wherein R<sup>3</sup> is hydrogen, and R<sup>1</sup> and R<sup>2</sup> taken together form the heterocyclic moiety of formula (a) and compounds have the structure of Formula IVa or IVb:

or a pharmaceutically acceptable sal thereof.

- 19. (Previously presented) The compound of claim 15, wherein
- i)  $R^1$  and  $R^2$  taken together form the heterocyclic moiety of formula (a); where  $R^X$  is defined according to one of the following groups:
  - (a) hydrogen or optionally substituted C1-6aliphatic;
  - (b) hydrogen, methyl, ethyl, propyl, n-butyl, tert-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl,  $C_{1-6}$ alkyl substituted with  $N(R)_2$ , or  $C_{1-6}$ alkyl substituted with  $Ar^1$ ; or

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- (c) hydrogen, methyl, or  $C_{1-2}$ ilkyl substituted with a group selected from optionally substituted phenyl, pyridyl, morpholino, piperidinyl, or piperazinyl.
- ii) R3 is defined according to one of the following groups:
  - (a) hydrogen, halogen, QR or QAr<sup>1</sup>, wherein Q is a C<sub>1-3</sub> alkylidene chain wherein one methylene unit of Q is optionally replaced by -O-, -S-, -NHCO-, or -NR-, and Ar<sup>1</sup> is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
  - (b) hydrogen, OH, OCH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>, NHCOMe, NH<sub>2</sub>, NH(C<sub>1-4</sub> aliphatic), N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, O(CH<sub>2</sub>)<sub>2</sub>morpholin-4-yl, O(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, O(CH<sub>2</sub>)<sub>2</sub>NH(C<sub>1-4</sub> aliphatic), O(CH<sub>2</sub>)<sub>2</sub>N(C<sub>1-4</sub> aliphatic)<sub>2</sub>, bromo, chloro, or fluoro; or (c) hydrogen;
- iii) R<sup>4</sup> is defined according to one of the following groups:
  - (a) a 6-membered saturated, partially unsaturated, or aryl ring having 0-3 nitrogens, a 9-10 membered bicyclic aryl ring having 0-2 nitrogens, or a 5 membered heteroaryl ring having 2-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is optionally substituted with  $(ZR^5)_m$ ;
  - (b) an optionally substituted ring selected from phenyl, cyclohexyl, naphthyl, pyridyl, pyrimidinyl, triazir,yl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, indazolyl, or benzimidazolyl, wherein said ring is optionally substituted with  $(ZR^5)_m$ ; or
  - (c) an optionally substituted phenyl group, wherein said phenyl group is optionally substituted with  $(ZR^5)_m$ ;
- iv) W1, W2 and W3 are defined according to one of the following groups:
  - (a) W<sup>1</sup> is nitrogen or CH, W<sup>2</sup> is nitrogen or C-(U)<sub>p</sub>R<sup>U</sup>, and W<sup>3</sup> is nitrogen or C-(V)<sub>q</sub>R<sup>V</sup>;

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- (b)  $W^1$  is nitrogen or CH,  $W^2$  is C-(U)<sub>p</sub> $R^U$ , and  $W^3$  is C-(V)<sub>q</sub> $R^V$ ; or
- (c) W1 is nitrogen or CH and W2 and W3 are each CH; and
- v) (U)<sub>p</sub>R<sup>U</sup> and (V)<sub>q</sub>R<sup>V</sup> groups are defined according to one of the following groups:
  - (a) hydrogen, halogen, NO<sub>2</sub>, CN, OR, SR or N(R)<sub>2</sub>, or C<sub>1.4</sub>aliphatic optionally substituted with oxo, OR, SR, N(R)<sub>2</sub>, halogen, NO<sub>2</sub> or CN;
  - (b) hydrogen, Me, OH, OMe or N(R)2; or
  - (c) both  $(U)_p R^U$  and  $(V)_q R^V$  are hydrogen.
- 20. (Previously presented) The compound of any one of claims 16, 17, 18 or 19, wherein each occurrence of Z is independently a bond or a C<sub>1-4</sub> alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -S-, -SO<sub>2</sub>-, or -NH-; and each occurrence of R<sup>5</sup> is independently hydrogen, C<sub>1-6</sub> aliphatic, halogen, NO<sub>2</sub>, OR, N(R)<sub>2</sub>, or optionally substituted phenyl, pyridyl, and pyrimidinyl
- 21. (Previously presented) The compound of claim 20, wherein each occurrence of ZR<sup>5</sup> is independently Cl, F, Br, methyl, ethyl, t-butyl, isopropyl, cyclopropyl, nitro, CN, OMe, OEt, CF<sub>3</sub>, NH<sub>2</sub>, phenyl, benzyl, benzyloxy, OH, methylenedioxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, CO<sub>2</sub>Me, phenoxy, O-pyridinyl, SO<sub>2</sub>phenyl, nitrophenoxy, aminophenoxy, S-dimethylpyrimidine, NH-methoxyphenyl, pyridinyl, phenol, chloro-fluoro-phenyl, dimethylphenyl, chlorophenyl, fluorophenyl, methoxyphenoxy, chlorophenoxy, ethoxyphenoxy, or fluorophenoxy.
- 22. (Previously presented) The compound of claim 18 having the formula **IVa**, wherein R<sup>X</sup> is hydrogen or optionally substituted C<sub>1.6</sub>aliphatic; m is 0, 1 or 2; and ZR<sup>5</sup> is Cl, F, Br, methyl, ethyl, t-butyl, isopropyl, cyclopropyl, nitro, CN, OMe, OEt, CF<sub>3</sub>, NH<sub>2</sub>, phenyl, benzyl, benzyloxy, OH, methylenedioxy, SO<sub>2</sub>NH<sub>2</sub>, CONH<sub>2</sub>, CO<sub>2</sub>Me, phenoxy, O-pyridinyl, SO<sub>2</sub>phenyl, nitrophenoxy, aminophenoxy, S-dimethylpyrimidine, NHphenyl, NH-methoxyphenyl, pyridinyl, phenol, chloro-fluoro-phenyl, dimethylaminophenyl, CF<sub>3</sub>-phenyl,

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dimethylphenyl, chlorophenyl, fluorophenyl, methoxyphenoxy, chlorophenoxy, ethoxyphenoxy, or fluorophenoxy.

23. (Previously presented) The compound of claim 1, selected from one of the following compounds:

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IVa-63

IVa-67 IVa-68

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IVb-5

**IVb-6** 

IVb-4

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OF

IVb-72.

(Original) A pharmaceutical composition comprising a compound according to claim
 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

25-27. (Canceled)

- 28. (Currently amended) A method of treating or lessening the severity of a disease or disorder selected from an allergic or type I hypersensitivity reaction, asthma, transplant rejection, graft versus host disease, or rheumatoid arthritis, or leukemia, comprising administering to a subject in need thereof a compound of claim 1 or a composition comprising said compound.
- 29. (Currently amended) The method of claim 28, comprising the further step of administering to said patient an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, a treatment for asthma, an anti-inflammatory agent, or an immunomodulatory or immunosuppressive agent, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

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